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Published in:
Tetrahedron-Asymmetry

DOI:
10.1016/S0957-4166(01)00453-0

Publication date:
2001

Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2497–2499

TETRAHEDRON: *ASYMMETRY*

Phosphonite ligands for enantioselective copper(I)-catalysed conjugate addition of diethylzinc to enones

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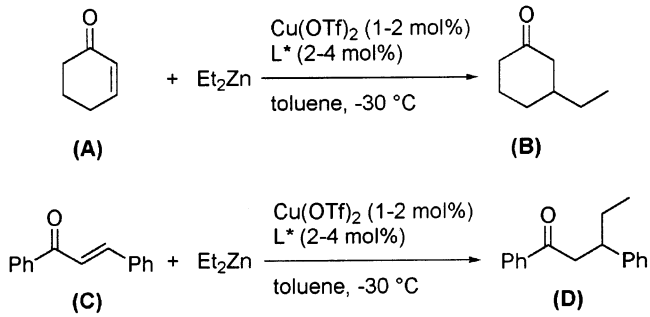
Received 9 October 2001; accepted 16 October 2001

Abstract—A wide variety of novel chiral monodentate phosphonite ligands derived from binaphthol and biphenanthrol have been tested as ligands in the copper(I)-catalysed conjugate addition of diethylzinc to enones, resulting in e.e.s of up to 82% for chalcone.

The conjugate addition of a carbon nucleophile to an α,β-unsaturated compound is one of the most important C–C bond-forming strategies available in organic synthesis.[1] The enantioselective copper(I)-catalysed 1,4-addition of organozinc reagents to cyclic or acyclic enones is particularly successful.[2] Traditionally, phosphorus(III) ligands are considered to be among the best soft ligands for copper(I) and a significant number of complexes, mainly with monodentate ligands, has been described.[3] Since the first reported copper-catalysed conjugate addition of diethylzinc to cyclohexenone using a phosphorus(III) ligand,[4] many efforts have been directed towards the development of efficient chiral phosphorus(III) ligands for this process. A breakthrough in catalytic enantioselective 1,4-additions was achieved using phosphoramidites as chiral ligands.[5] Excellent enantioselectivities have subsequently been obtained using several homochiral phosphorus amidites,[6a–c] phosphites,[6d–f] amido-phosphines[6g] and oxazoline-phosphites.[6h–i] Despite their success in asymmetric hydrosilylation[7] and hydrogenation,[8] phosphonites have received little attention for copper-catalysed conjugate addition of diethylzinc to enones. The group of Reetz have reported the successful application of a bidentate ferrocene phosphonite resulting in 96% e.e. in the 1,4-addition of diethylzinc to 2-cyclohexenone.[9] Recently, TADDOL-derived phosphonites have been shown to give a moderate degree of enantioselectivity.[10] In this context, we report the use of binaphthol- and biphenanthrol-derived monophosphonites in the conjugate addition of diethylzinc to 2-cyclohexenone **A** and chalcone **C** (Scheme 1).

All ligands used in this study are based on binaphthol **1n–5n** or biphenanthrol **1p–5p** with different exocyclic substituents (aryl or alkyl). Diphosphonite **6n** is based on binaphthol with a two carbon backbone (Fig. 1). The chiral ligands were readily prepared by condensation of the dichlorophosphine precursor with the corresponding biphenol.[11]

All the experiments were performed under identical conditions. $Cu(OTf)_2$ (1–2 mol%) and the chiral phosphonite (1:2 ratio for monodentate and 1:1 for bidentate) were dissolved in toluene and stirred for 1 h at room temperature, after which the substrate **A** or **C** was added and the reaction mixture cooled to −30°C. After stirring the mixture for a further 10 min, diethylzinc was added and stirring was continued.



Scheme 1.

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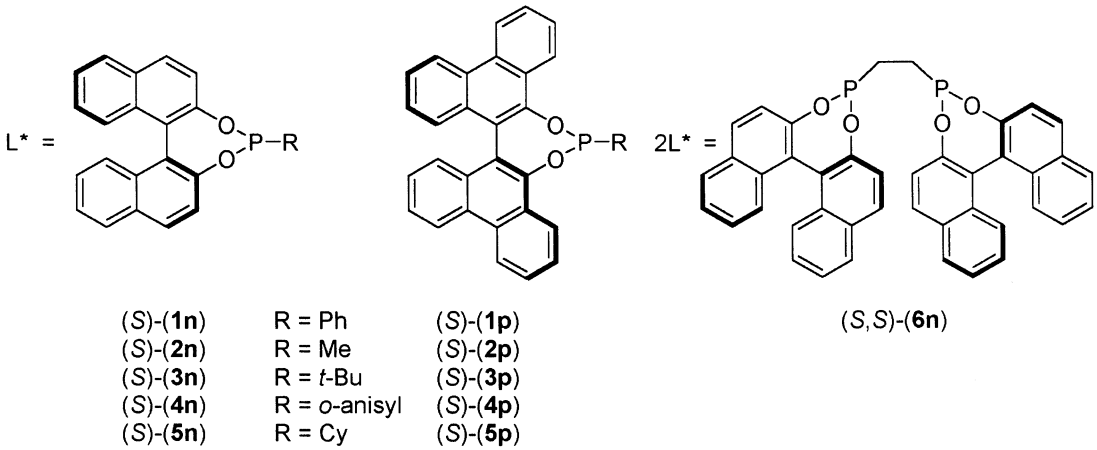
PII: S0957-4166(01)00453-0



(*S*)-(**1n**)	R = Ph	(*S*)-(**1p**)
(*S*)-(**2n**)	R = Me	(*S*)-(**2p**)
(*S*)-(**3n**)	R = *t*-Bu	(*S*)-(**3p**)
(*S*)-(**4n**)	R = *o*-anisyl	(*S*)-(**4p**)
(*S*)-(**5n**)	R = Cy	(*S*)-(**5p**)

(*S,S*)-(**6n**)

Figure 1.

Table 1. Enantioselective conjugate addition of diethylzinc to cyclohexenone **A** catalysed by $Cu(OTf)_2$ and phosphonites **1n**–**6n** and **1p**–**5p**

Entry	Ligand	Time (h)	Conversion (%)[d]	E.e. (%)[d]
1[a]	(*S*)-**1n**	16	100	18 (*S*)
2[b]	(*S*)-**2n**	16	100	29 (*S*)
3[b]	(*S*)-**3n**	1	100	30 (*S*)
4[b]	(*S*)-**4n**	3	>99	17 (*S*)
5[b]	(*S*)-**5n**	16	>99	9 (*S*)
6[b]	(*S,S*)-**6n**	3	94	19 (*S*)
7[a]	(*R*)-**1p**	16	100	41 (*R*)
8[b]	(*S*)-**2p**	3	>99	29 (*S*)
9[b]	(*S*)-**3p**	1	100	29 (*S*)
10[b]	(*S*)-**4p**	3	75	38 (*S*)
11[b]	(*S*)-**5p**	1	>99	36 (*S*)
12[c]	(−)-TADDOL-Ph	2	97	54 (*S*)

[a] *Reaction conditions*: $Cu(OTf)_2$ (1 mol%), 2 L (2 mol%), toluene (10 mL), −30°C.

[b] *Reaction conditions*: $Cu(OTf)_2$ (2 mol%), 2 L (4 mol%), toluene (5 mL), −30°C.

[c] Data from Ref. 10.

[d] Conversion and e.e. determined by GC using *n*-dodecane as internal standard.[12a]

The results for 2-cyclohexenone **A** are summarised in Table 1. With all the ligands studied, moderate (up to 41% e.e.) to poor enantioselectivities were obtained. For the n ligands (ligands with binaphthyl moiety), those with alkyl exocyclic substituents give better e.e.s than those with aryl substituents (compare entries 2 and 3 with 1 and 4). For the p ligands (ligands based on biphenanthrol), the trend seems to be the other way round: aryl substituents in the ligand result in better e.e.s than alkyl substituents (compare entries 7 and 10 with 8 and 9). Both ligands with a cyclohexyl group seem to be an exception to this rule. No clear pattern emerges on comparing different biphenol moieties for the ligands; ligand **1p**, derived from biphenanthrol and phenyl, gives the highest enantioselectivity (41%) of all the ligands tested. The ligands which induced the fastest reactions are the ones with *tert*-butyl as the R group, **3n** and **3p**, with complete ethyl transfer after 1 h (entries 3 and 9).

For the conjugate addition of diethylzinc to acyclic enones, chalcone **C** was chosen as a model substrate. All phosphonites show moderate to high enantioselectivity. The results are shown in Table 2. The reactions went to completion after 16 h as judged by TLC. Ligands with sterically demanding alkyl groups (e.g. ligands with *tert*-butyl and cyclohexyl substituents) induce high enantioselectivities (entries 3, 5, 9 and 11). For instance, ligand **3n** induces the highest e.e. so far obtained for acyclic enones using phosphonite ligands (82%, entry 3). Introduction of *ortho* substituents such as OMe onto the aryl group, does not have a consistent effect on the enantioselectivity: low e.e.s are obtained with the n ligand (compare entry 1 with 4), but an increase is noticed when the p ligand is used (compare entry 7 with 10). The bidentate ligand **6n** performed significantly worse than most monodentate ligands, giving only 43% e.e. It should be noted that under similar

Table 2. Enantioselective conjugate addition of diethylzinc to chalcone (**C**) catalysed by $Cu(OTf)_2$ and phosphonites (**1n**)–(**6n**) and (**1p**)–(**5p**)[a]

Entry	Ligand	E.e. (%)[b]
1	(*S*)-**1n**	63 (*R*)
2	(*S*)-**2n**	43 (*R*)
3	(*S*)-**3n**	82 (*R*)
4	(*S*)-**4n**	47 (*R*)
5	(*S*)-**5n**	60 (*R*)
6	(*S,S*)-**6n**	43 (*R*)
7	(*R*)-**1p**	53 (*S*)
8	(*S*)-**2p**	63 (*R*)
9	(*S*)-**3p**	80 (*R*)
10	(*S*)-**4p**	63 (*R*)
11	(*S*)-**5p**	74 (*R*)
12[c]	(−)-TADDOL-Ph	7 (*R*)

[a] *Reaction conditions*: $Cu(OTf)_2$ (2 mol%), 2 L (4 mol%), toluene (5 mL), −30°C.

[b] E.e. determined by HPLC.[12b]

[c] Data from Ref. 10. *Conditions*: −5°C to rt, 24 h.

conditions, biphenol-based phosphonites induce much higher enantioselectivity (82% versus 7%) than those reported for phosphonites based on the TADDOL backbone (compare with entry 12).[10]

In conclusion, we have presented the application of some novel phosphonite ligands in the copper-catalysed conjugate addition of diethylzinc to enones (cyclic and acyclic) displaying moderate to high e.e.s. The best results are obtained for acyclic enones; 82% e.e. is the highest obtained so far with monodentate phosphonite ligands in the asymmetric 1,4-addition of diethylzinc to chalcone. The fact that the enantioselectivity only depends on the biaryl unit in all the ligands presented here and due to the modularity of these ligands, it should be easy to vary further the nature of the exocyclic group, introducing another element of chirality, in order to achieve even higher enantioselectivity.

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12. (a) GC analysis were carried out using a HP5890 II GC equipped with a HP3396 series II integrator and a Chiraldex GTA column (isothermic at 100°C); (b) HPLC analysis were performed using a Waters 600E HPLC with a 99 diode array detector and a Chiracel OD column.